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Historical epidemiology of hepatitis C virus (HCV) in select countries – volume 3

V. Liakina,[1,2,‡] S. Hamid,[3,‡] J. Tanaka,[4,‡] S. Olafsson,[5,‡] A. I. Sharara,[6,‡] S. M. Alavian,[7,8,‡] L. Gheorghe,[9,‡] E. S. El Hassan,[10,‡] F. Abaalkhail,[11] Z. Abbas,[12] A. Abdou,[10] A. Abourached,[13,‡] F. Al Braiki,[14] F. Al Hosani,[15] K. Al Jaberi,[16] M. Al Khatry,[17] M. A. Al Mulla,[15] H. Al Quraishi,[18] A. Al Rifai,[19] Y. Al Serkal,[20] A. Alam,[21] H. I. Alashgar,[22] S. Alawadhi,[10] L. Al-Dabal,[23] P. Aldins,[24] F. Z. Alfaleh,[25,‡] A. S. Alghamdi,[26] R. Al-Hakeem,[27] A. A. Aljumah,[28] A. Almessabi,[14] A. N. Alqutub,[26] K. A. Alswat,[29] I. Altraif,[28] M. Alzaabi,[30,‡] N. Andrea,[31] A. M. Assiri,[27,‡] M. A. Babatin,[26] A. Baqir,[32] M. T. Barakat,[33] O. M. Bergmann,[34] A. R. Bizri,[35] S. Blach,[36] A. Chaudhry,[37] M. S. Choi,[38] T. Diab,[39] S. Djauzi,[40] S. El Khoury,[41] C. Estes,[36] S. Fakhry,[42] J. I. Farooqi,,[43,44] H. Fridjonsdottir,[45] R. A. Gani,[40] A. Ghafoor Khan,[46] A. Goldis,[47,‡] M. Gottfredsson,[48] S. Gregorcic,[49] B. Hajarizadeh,[50,51,‡] K. H. Han,[52,‡] I. Hasan,[40] A. Hashim,[53] G. Horvath,[54] B. Hunyady,[55,56,‡] R. Husni,[57] W. Jafri,,[58,‡] A. Jeruma,[59,60] J.G. Jonasson,[45,61,62] B. Karlsdottir,[63] D. Y. Kim,[52,‡] Y. S. Kim,[64] Z. Koutoubi,[65] L. A. Lesmana,[40,66,‡] Y. S. Lim,[67] A. Löve,[48,68] M. Maimets,[69] M. Makara,[70,‡] R. Malekzadeh,[71] M. Matičič,[49,‡] M. S. Memon,[72] S. Merat,[71] J. E. Mokhbat,[73] F. H. Mourad,[6] D. H. Muljono,[74,75] A. Nawaz,[76] N. Nugrahini,[77,‡] S. Priohutomo,[78] H. Qureshi,[79] P. Rassam,[41] H. Razavi,[36] D. Razavi-Shearer,[36] K. Razavi-Shearer,[36] B. Rozentale,[59,60] M. Sadik,[72] K. Saeed,[80] A. Salamat,[81] R. Salupere,[69,‡] F. M. Sanai,[25] A. Sanityoso Sulaiman,[40] R. A. Sayegh,[82] J. D. Schmelzer,[36] A. Sibley,[36] M. Siddiq,[83,84] A. M. Siddiqui,[85] G. Sigmundsdottir,[86] B. Sigurdardottir,[63] D. Speiciene,[1] A. Sulaiman,[40,87] M. A. Sultan,[88] M. Taha,[89] H. Tarifi,[90] G. Tayyab,[91,92] I. Tolmane,[59,60,‡] M. Ud din,[93] M. Umar,[94,95] J. Valantinas,[1,‡] J. Videčnik-Zorman,[49] C. Yaghi,[82] E. Yunihastuti,[96] M. A. Yusuf,[97] B. F. Zuberi[98] and J. Gunter[36] [1]*Centre of Hepatology, Gastroenterology, and Dietetics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;* [2]*Department of Biomechanics, Vilnius Gediminas Technical University, Vilnius, Lithuania;* [3]*The Aga Khan University, Karachi, Pakistan;* [4]*Department of Epidemiology, Infectious Disease Control and Prevention, Hiroshima University Institute of Biomedical and Health Sciences, Hiroshima, Japan;* [5]*Division of Gastroenterology and Hepatology, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [6]*Division of Gastroenterology, American University of Beirut Medical Center, Beirut, Lebanon;* [7]*Baqiatallah Research Center for Gastroenterology and Liver Diseases, Baqiatallah University of Medical Sciences, Tehran, Iran ;* [8]*Middle East Liver Diseases Centre, Tehran, Iran;* [9]*Center of Gastroenterology & Hepatology, Fundeni Clinical Institute, Bucharest, Romania;* [10]*Rashid Hospital, Dubai Health Authority, Dubai, UAE;* [11]*Department of Liver and Small Bowel Transplantation,King Faisal Specialist Hospital and Research Center, Alfaisal University,Riyadh, Saudi Arabia;* [12]*Ziauddin University, Karachi, Pakistan;* [13]*National Hepatitis Program, Ministry of Public Health, Beirut, Lebanon;* [14]*Abu Dhabi Health Services Company, Abu Dhabi, UAE;* [15]*Communicable Diseases Department, Health Authority Abu Dhabi, Abu Dhabi, UAE;* [16]*Health Regulation Division, Health Authority Abu Dhabi, Abu Dhabi, UAE;* [17]*Ras Al Khaimah Hospital, Ras Al Khaimah, UAE;* [18]*Dubai Health Authority, Dubai, UAE;* [19]*Mafraq Hospital, Abu Dhabi, UAE;* [20]*Hospitals Sector, Ministry of Health, Al-Ain, UAE;* [21]*Shaikh Zayed Hospital, Lahore, Pakistan;* [22]*Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;* [23]*Department of Pulmonary Medicine, Rashid Hospital, Dubai Health Authority, Dubai, UAE;* [24]*Infection Control Department, Pauls Stradins Clinical University Hospital, Riga, Latvia;* [25]*Liver Disease Research Center, King Saud University, Riyadh, Saudi Arabia;* [26]*Gastroenterology and Hepatology Unit, Medical Specialties Department, King Fahad Hospital, Riyadh, Saudi Arabia;* [27]*Department of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia;* [28]*King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia;* [29]*Department of Medicine, King Saud University Liver Disease Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia;* [30]*Zayed Military Hospital, Abu Dhabi, UAE;* [31]*Daman National Health Insurance Company, Abu Dhabi, UAE;* [32]*Seyal Medical Centre, Multan, Pakistan;* [33]*Health Authority Abu Dhabi, Abu Dhabi, UAE;* [34]*Division of Gastroenterology and Hepatology, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [35]*Faculty of Medicine, Division of Infectious Diseases, American University of Beirut Medical Center, Beirut, Lebanon;* [36]*Center for Disease Analysis (CDA), Louisville, CO, USA;* [37]*Gujranwala Liver Foundation, Siddiq Sadiq Hospital, Gujranwala, Pakistan;* [38]*Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea;* [39]*Al Ain Hospital, Al Ain, UAE;* [40]*Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia;* [41]*Gastroenterology Department, Saint George Hospital, University of Balamand, Balamand, Lebanon;* [42]*Abu Dhabi Police, Abu Dhabi, UAE;* [43]*Postgraduate Medical Institute, Khyber Medical University, Peshawar, Pakistan;*

[44]*Government Lady Reading Hospital, Peshawar, Pakistan;* [45]*Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [46]*Department of Gastroenterology & Hepatology, Lady Reading Hospital, Peshawar, Pakistan;* [47]*Clinic of Gastroenterology, University of Medicine 'Victor Babes', Timisoara, Romania;* [48]*Faculty of Medicine, School of Health Sciences, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [49]*Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre, Ljubljana, Slovenia;* [50]*The Kirby Institute, University of New South Wales Australia, Sydney, NSW, Australia;* [51]*The Australian Research Centre in Sex, Health and Society, La Trobe University, Melbourne, VIC, Australia;* [52]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea;* [53]*Liver Transplantation, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;* [54]*Hepatology Center of Buda, Budapest, Hungary;* [55]*Department of Gastroenterology, Somogy County Kaposi Mor Teaching Hospital, Kaposvar, Hungary;* [56]*First Department of Medicine, University of Pecs, Pecs, Hungary;* [57]*Lebanese American University Medical Center, Rizk Hospital, Beirut, Lebanon;* [58]*Aga Khan University, Karachi, Pakistan;* [59]*Department of Hepatology, Infectology Center of Latvia, Riga, Latvia;* [60]*Department of Infectology and Dermatology, Riga Stradins University, Riga, Latvia;* [61]*Icelandic Cancer Registry, Reykjavik, Iceland;* [62]*The Faculty of Medicine, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [63]*Division of Infectious Disease, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [64]*Department of Internal Medicine, Soon Chun Hyang University Bucheon Hospital, Bucheon, Korea;* [65]*Digestive Disease Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE;* [66]*Digestive Disease and GI Oncology Center, Medistra Hospital, Jakarta, Indonesia;* [67]*Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea;* [68]*Department of Virology, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland;* [69]*University of Tartu, Tartu University Hospital, Tartu, Estonia;* [70]*Central Outpatient Clinic, Saint Laszlo Hospital, Budapest, Hungary;* [71]*Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran;* [72]*Asian Institute of Medical Science (AIMS), Hyderabad, Pakistan;* [73]*Division of Infectious Diseases and Division of Clinical Microbiology, Lebanese American University Medical Center Rizk Hospital, Beirut, Lebanon;* [74]*Eijkman Institute for Molecular Biology, Jakarta, Indonesia;* [75]*Department of Hepatitis & Emerging Infectious Diseases, University of Sydney, Sydney,NSW, Australia;* [76]*Department of Gastroenterology, Fatima Memorial Hospital College of Medicine and Dentistry, Lahore, Pakistan;* [77]*Sub-Directorate for Gastrointestinal Infection, Diarrheal Diseases, and Hepatitis, Directorate of Direct Transmitted Disease Control, Disease Control & Environmental Health, Ministry of Health, Jakarta, Indonesia;* [78]*Directorate of Direct Transmitted Disease Control, Disease Control & Environmental Health, Ministry of Health, Jakarta, Indonesia;* [79]*Pakistan Medical Research Council, Islamabad, Pakistan;* [80]*Khawar Clinic, Sahiwal, Pakistan;* [81]*Department of Gastroenterology, Military Hospital, Rawalpindi, Pakistan;* [82]*Department of Hepatology and Gastroenterology, School of Medical Science, Saint Joseph University, Beirut, Lebanon;* [83]*Jinnah Memorial Hospital, Rawalpindi, Pakistan;* [84]*Yusra Medical College, Rawalpindi, Pakistan;* [85]*Allama Iqbal Medical College, Lahore, Pakistan;* [86]*Centre for Health Security and Communicable Disease Control, Directorate of Health in Iceland, Reykjavik, Iceland;* [87]*Klinik Hati Prof. Ali Sulaiman, Jakarta, Indonesia;* [88]*Health Funding Department, Enaya Insurance Company, Abu Dhabi, UAE;* [89]*Department of Medicine, Tawam Hospital, Al Ain, UAE;* [90]*Pharmacy Department, Tawam Hospital, Al Ain, UAE;* [91]*Postgraduate Medical Institute, Lahore General Hospital, Lahore, Pakistan;* [92]*Doctors Hospital and Medical Center, Lahore, Pakistan;* [93]*Pakistan Society of Gastroenterology, Karachi, Pakistan;* [94]*Department of Medicine, Rawalpindi Medical College, Rawalpindi, Pakistan;* [95]*Department of Medicine, Holy Family Hospital, Rawalpindi, Pakistan;* [96]*Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;* [97]*Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan; and* [98]*Dow Medical College, Karachi, Pakistan*

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SUMMARY. Detailed, country-specific epidemiological data are needed to characterize the burden of chronic hepatitis C virus (HCV) infection around the world. With new treatment options available, policy makers and public health officials must reconsider national strategies for infection control. In this study of 15 countries, published and unpublished data on HCV prevalence, viraemia, genotype, age and gender distribution, liver transplants and diagnosis and treatment rates were gathered from the literature and validated by expert consensus in each country. Viraemic prevalence in this study ranged from 0.2% in Iran and Lebanon to 4.2% in Pakistan. The largest viraemic populations were in Pakistan (7 001 000 cases) and Indonesia (3 187 000 cases). Injection drug use (IDU) and a historically unsafe blood supply were major risk factors in most countries. Diagnosis, treatment and liver transplant rates varied widely between countries. However, comparison across countries was difficult as the number of cases changes over time. Access to reliable data on measures such as these is critical for the development of future strategies to manage the disease burden.

Abbreviations: G, genotype; HCV, hepatitis C virus; IDU, injection drug use; Peg-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; UN, United Nations.

Correspondence: Homie Razavi, Center for Disease Analysis, Louisville, CO 80026, USA.
E-mail: homie.razavi@centerforda.com
‡Denotes senior authors

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INTRODUCTION

Hepatitis C virus (HCV) infection is a global public health burden, causing an increasing level of liver-related morbidity and mortality due to the disease progression of an ageing-prevalent population [1–6]. The HCV disease paradigm varies by country based on historical and present risk factors, screening programmes and treatment rates. Individual countries must consider appropriate country-specific prevention, diagnosis and treatment strategies to reduce the disease burden represented by HCV. Unfortunately, in many countries, there is a lack of robust epidemiological data upon which to base these strategies. Many studies have examined regional HCV infection rates [7–12], but they have typically focused on quantifying the anti-HCV prevalence. This study is a continuation of a project to quantify global HCV epidemiology in a systematic manner. The aim of this study was to develop consensus estimates, using the best available published and unpublished data, for the total number of viraemic infections [HCV ribonucleic acid (RNA) positive], the total number of viraemic-diagnosed individuals, the number of viraemic newly diagnosed, annual number of treated patients and the number of liver transplants attributed to HCV in each country. The countries were selected based on the availability of published data and the willingness to collaborate. Other countries are being analysed and will be published separately.

METHODOLOGY

A systematic review of the literature was conducted to identify studies reporting the total number of HCV cases diagnosed, treated and cured in each country of interest. The review encompassed all studies between January 1990 and December 2014. Indexed articles were found by searching PubMed and Embase. Nonindexed sources were identified through individual countries' Ministry of Health websites and international agencies' reports. In addition, an expert panel in each country provided proceedings of local conferences, unpublished data and data from large liver centres that could be extrapolated to the national level.

Face-to-face meetings were conducted to review findings and analyses with the expert panel. When no input data were available, analogues (data from countries with a similar healthcare practice and/or risk factors) or expert inputs were used. Ranges were chosen to capture uncertainty in inputs, with wider ranges implying greater uncertainty.

Viraemic infections represented current RNA-positive HCV or chronic HCV infections. The term viraemic was used throughout this study to highlight the presence of HCV virus. The term new infections was used for acute infections among immigrants entering the country. The term incidence was used for acute infections and not newly diagnosed. Care was taken to collect and list the year of the reported collection as the data were reported over a wide range of years. As shown in the next publication in this supplement [13], a modelling approach was used to estimate the HCV-infected populations (viraemic, diagnosed and treated) in 2014. Unless stated, population data were obtained from the United Nations' (UN) population database by age, gender and five-year age-cohort [14].

The annual number of liver transplants was gathered from national or international databases and adjusted for the percentage attributed to HCV. The number of antibody-positive and RNA-positive diagnosed cases was gathered from national databases, use of analogues or expert panel input. It was explicitly stated when published or official data were not available. In countries where HCV was a notifiable infection and a reliable annual number of newly diagnosed cases were reported, the total of diagnosed cases was calculated by summing data from all years after taking into consideration the mortality among the diagnosed cases. In countries where the number of total and newly diagnosed cases was not available, expert panel input was used. Diagnosis rates from the known countries (analogues) were provided to the expert panel, and the panel selected one or more countries that had similar profiles. It was assumed that the viraemic rate among the diagnosed population was the same as the total infected population, and the same viraemic rate was used to estimate the number of viraemic-diagnosed individuals.

Two methods were used to estimate the total number of treated HCV-infected patients. In countries where reliable national data were available, the reported numbers were used. In other countries, the annual number of units of pegylated interferon (Peg-IFN) or ribavirin (RBV) sold, as reported by IMS Health [15], were converted to treated patients using the average number of units per patient. The average number of units per patient was calculated using the genotype distribution of the infected population (assumed the genotype distribution of the treated population was the same as the overall population), the duration of treatment for each genotype, the number of Peg-IFN or RBV units per week and the percentage of patients who completed their treatment (80% in most countries unless stated otherwise). The annual number of units was

adjusted using inputs from the expert panel to account for uses other than HCV as well as potential under-reporting.

RESULTS

Table 1 includes the results of the literature review for all 15 countries in this analysis, including estimates of antibody and viraemic prevalence, genotype distribution, viraemic diagnosis, annual treatment and liver transplants. The specific age and gender distribution of the viraemic-prevalent population for each country is shown in Fig. 1.

Estonia

HCV-infected population

HCV epidemiology data are sparse in Estonia. The prevalence of anti-HCV was estimated between 1.5% and 2.4%, in 2013, with a viraemic prevalence of 1.5% (1.1–1.9%) (expert consensus). The viraemic rate was estimated through expert consensus to be 76%. The age and gender distribution was estimated using annual notification data from 2000 to 2013 [16]. The notified population was aged to the year 2013, accounting for mortality and cured patients. Multiple genotype studies were available, with the most recent estimate chosen for consideration in the model [17].

Diagnosed

As of 2014, approximately 9600 viraemic cases were diagnosed (50%) (expert consensus). Annually, 190 viraemic cases are newly diagnosed [16].

Treated

In 2014, approximately 500 patients were treated for HCV. Of these, 34 ≥F3 patients were treated with boceprevir, 39 ≥F3 patients were treated with telaprevir, and the remainder of patients ≥F0 were treated with Peg-IFN/Riba [18].

Liver transplants

Data on the annual number of liver transplants and liver transplants attributable to HCV were available from the Transplantation Centre of Tartu University Hospital. Tartu University Hospital is the only hospital in Estonia where organ transplants are performed. In 2014, 10 liver transplants were performed, with four (40%) attributable to HCV.

Hungary

HCV-infected population

HCV epidemiology data are sparse in Hungary. The prevalence of anti-HCV was estimated at 0.70% (0.5–0.9%) based on expert consensus. A viraemic rate of 75%, provided by experts, was applied. The total viraemic population in 2014 was estimated at 52 000 (39 000–65 000) individuals, corresponding to a viraemic prevalence of 0.5% (0.4–0.7%). The age and gender distribution of the infected population was constructed using unpublished data from the Hungary treatment registry, which was provided through personal communication with experts (Makara 2015 personal communication). The genotype distribution in the prevalent population was estimated using data from both non-IDU and IDU sources. The non-IDU genotype distribution was based on data presented at the 8th International Symposium on Molecular Diagnostics [19], with adjustment based on expert consensus to the distribution of G1 and G3. The genotype distribution for IDU was based on personal communication with experts (Makara 2015 personal communication) and was proportionally combined with the non-IDU genotype distribution to calculate a weighted overall distribution for the prevalent population.

Diagnosed

Estimates of the diagnosed population were based upon expert consensus. There were an estimated 20 900 previously diagnosed cases in 2010 and 2100 newly diagnosed cases.

Treated

According to expert input, it was estimated that between 1000 and 1200 patients were treated annually.

Liver transplants

Liver transplant data were available through an international organ registry for the years 1993 to 2013 [20]. In 2013, there were 45 liver transplants performed in Hungary. According to expert consensus, the number of liver transplants jumped to 70 in 2014. Experts estimate that 30% of liver transplants per year are attributable to HCV.

Iceland

HCV-infected population

Overall prevalence of anti-HCV in 2014 was estimated at 0.4% (0.3–0.5%). Based on expert consensus, approximately 80% of HCV cases have been diagnosed in Iceland. The total number of surviving diagnosed anti-HCV cases, excluding previously treated and cured patients, is estimated at 1080 based on data from the Centre for Health Security and Infectious Disease Control, equivalent to approximately 1400 prevalent cases after adjustment for the undiagnosed population. A viraemic rate of 80% was applied, and the total viraemic population in 2014 was estimated at 1100 (880–1300) individuals after accounting for treated and cured patients, corresponding to a viraemic prevalence of 0.3% (0.3–0.4%). Data from the Centre for Health Security and Infectious Disease Control were used to determine the age and gender distribution based on demographic data collected from surviving diagnosed cases during 1986 to August 2014. The genotype

Table 1 Hepatitis C virus (HCV) epidemiology by country

	Estonia	Hungary	Iceland	Indonesia	Iran	Japan	Latvia	Lebanon
Country's Population (000)	1300	9900	340	231 000	71 000	127 000	2100	4500
Year	2013	2014	2014	2007	2006	2011	2008	2011
HCV Antibody Positive (000)								
Total Cases	25 (19 - 31)	70 (52 - 87)	1.4 (1.1 - 1.6)	1848 (277 - 3857)	275 (189 - 360)	1789 (1443 - 2157)	51 (36 - 71)	9.3 (3.3 - 33)
Prevalence	2.0% (1.5% - 2.4%)	0.7% (0.5% - 0.9%)	0.4% (0.3% - 0.5%)	0.8% (0.1% - 1.7%)	0.4% (0.3% - 0.5%)	1.4% (1.1% - 1.7%)	2.4% (1.7% - 3.3%)	0.2% (0.1% - 0.7%)
Year of Estimate	2013	2014	2014	2007	2006	2011	2008	2011
Viremic Infections (000)								
Total Viremic Cases	19 (15 - 24)	52 (39 - 65)	1.1 (0.88 - 1.3)	1214 (182 - 2534)	170 (117 - 223)	1252 (1010 - 1510)	39 (26 - 50)	7.9 (2.8 - 28)
Viremic Prevalence	1.5% (1.1% - 1.9%)	0.5% (0.4% - 0.7%)	0.3% (0.3% - 0.4%)	0.5% (0.1% - 1.1%)	0.2% (0.2% - 0.3%)	1.0% (0.8% - 1.2%)	1.8% (1.2% - 2.4%)	0.2% (0.1% - 0.6%)
Viremic Rate (%)	76%	75%	80%	66%	62%	70%	71%	85%
Year of Estimate	2013	2014	2014	2007	2006	2011	2008	2011
Genotypes (%)								
1a	1%	9%	41%	26%	40%	-	46%	25%
1b	72%	80%	2%	39%	12%	65%	4%	17%
1 Other	-	2%	-	3%	1%	-	13%	-
1	73%	91%	43%	68%	53%	65%	64%	42%
2	3%	1%	1%	9%	1%	34%	4%	5%
3	24%	7%	55%	9%	28%	-	32%	8%
4	-	2%	1%	4%	1%	-	1%	46%
5	-	0%	-	-	-	-	-	1%
6	-	-	-	-	-	-	-	-
Other	-	-	-	10%	17%	1%	-	-
Year of Estimate	2007	2014	2013	2014	2004	1991 - 2013	2014	2014
Diagnosed (Viremic)								
Total Cases	9600	20 900	865	121 000	60 000	956 000	17 000	1600
Annual Newly Diagnosed	190	2100	60	12 100	6000	8000	1300	160
Year of Estimate	2014	2010	2013	2013	2013	2011	2010	2014
Treated								
Annual Number Treated	500	1200	30	230	4500	26 900	840	170
Year of Estimate	2014	2014	2011	2011	2011	2012	2014	2014
Liver Transplants								
Total Liver Transplants	10	70	45	13	590	447	1	15
HCV Liver Transplants	4	21	2	0	94	219	0	1
% due to HCV	40%	30%	4%	0%	16%	49%	0%	6.7%
Year of Estimate	2014	2014	1985 - 2013	2014	2013	2011	2011	1999-2008

(continued)

Table 1 *(continued)*

	Lithuania	Pakistan	Romania	Saudi Arabia	Slovenia	South Korea	UAE
Country's Population (000)	3000	167 000	22 000	19 300	2100	48 200	1100
Year	2013	2008	2008	2011	2014	2009	2014
HCV Antibody Positive (000)							
Total Cases	51 (31 - 70)	8010 (5792 - 9920)	719 (637 - 800)	143 (116 - 368)	8.3 (6.2 - 10)	478 (376 - 621)	16 (14 - 18)
Prevalence	1.7% (1.0% - 2.3%)	4.8% (3.5% - 5.9%)	3.3% (2.9% - 3.6%)	0.7% (0.6% - 1.9%)	0.4% (0.3% - 0.5%)	1.0% (0.8% - 1.3%)	1.5% (1.4% - 1.7%)
Year of Estimate	2013	2008	2008	2011	2014	2009	2014
Viremic Infections (000)							
Total Viremic Cases	33 (21 - 46)	7001 (5062 - 8670)	611 (541 - 680)	100 (81 - 257)	6.5 (4.9 – 8.1)	268 (211 - 349)	11 (10 - 12)
Viremic Prevalence	1.1% (0.7% - 1.5%)	4.2% (3.0% - 5.2%)	2.8% (2.5% - 3.1%)	0.5% (0.4% - 1.3%)	0.3% (0.2% - 0.4%)	0.6% (0.4% - 0.7%)	1.0% (0.9% - 1.1%)
Viremic Rate (%)	66%	87%	85%	70%	78%	56%	68%
Year of Estimate	2013	2008	2008	2011	2014	2009	2014
Genotypes (%)							
1a	2%	5%	5%	13%	14%	3%	8%
1b	69%	1%	93%	26%	23%	45%	13%
1 Other	4%	1%	-	-	19%	4%	28%
1	75%	7%	98%	39%	56%	53%	49%
2	6%	4%	-	4%	5%	45%	4%
3	19%	79%	1%	5%	38%	1%	17%
4	-	2%	1%	53%	1%	0%	30%
5	-	0%	-	-	-	-	-
6	-	0%	-	-	-	1%	-
Other	-	8%	-	-	-	-	-
Year of Estimate	2003 - 2009	1996 - 2011	2004-2008	2003	1993-2007	2013	2010
Diagnosed (Viremic)							
Total Cases	5000	1 050 000	90 000	20 100	3300	93 600	3600
Annual Newly Diagnosed	500	100 000	7500	2000	170	8000	360
Year of Estimate	2010	2010	2014	2013	2014	2012	2014
Treated							
Annual Number Treated	450	85 000	4100	1900	150	4500	140
Year of Estimate	2010	2011	2014	2009	2014	2011	2011
Liver Transplants							
Total Liver Transplants	12	300	124	146	31	1212	20
HCV Liver Transplants	5	225	33	72	2	59	12
% due to HCV	40%	75%	27%	49%	7%	5%	60%
Year of Estimate	2014	2012	2014	2012	2014	2011	2014

HCV antibody prevalence – prevalence of past or active HCV infection, viraemic prevalence – prevalence of active HCV infections, viraemic rate – percentage of past or active infections who have an active infection, viraemic-diagnosed individuals – the number of individuals diagnosed with an active infection, annual newly diagnosed – the number of active HCV infections diagnosed for the first time.

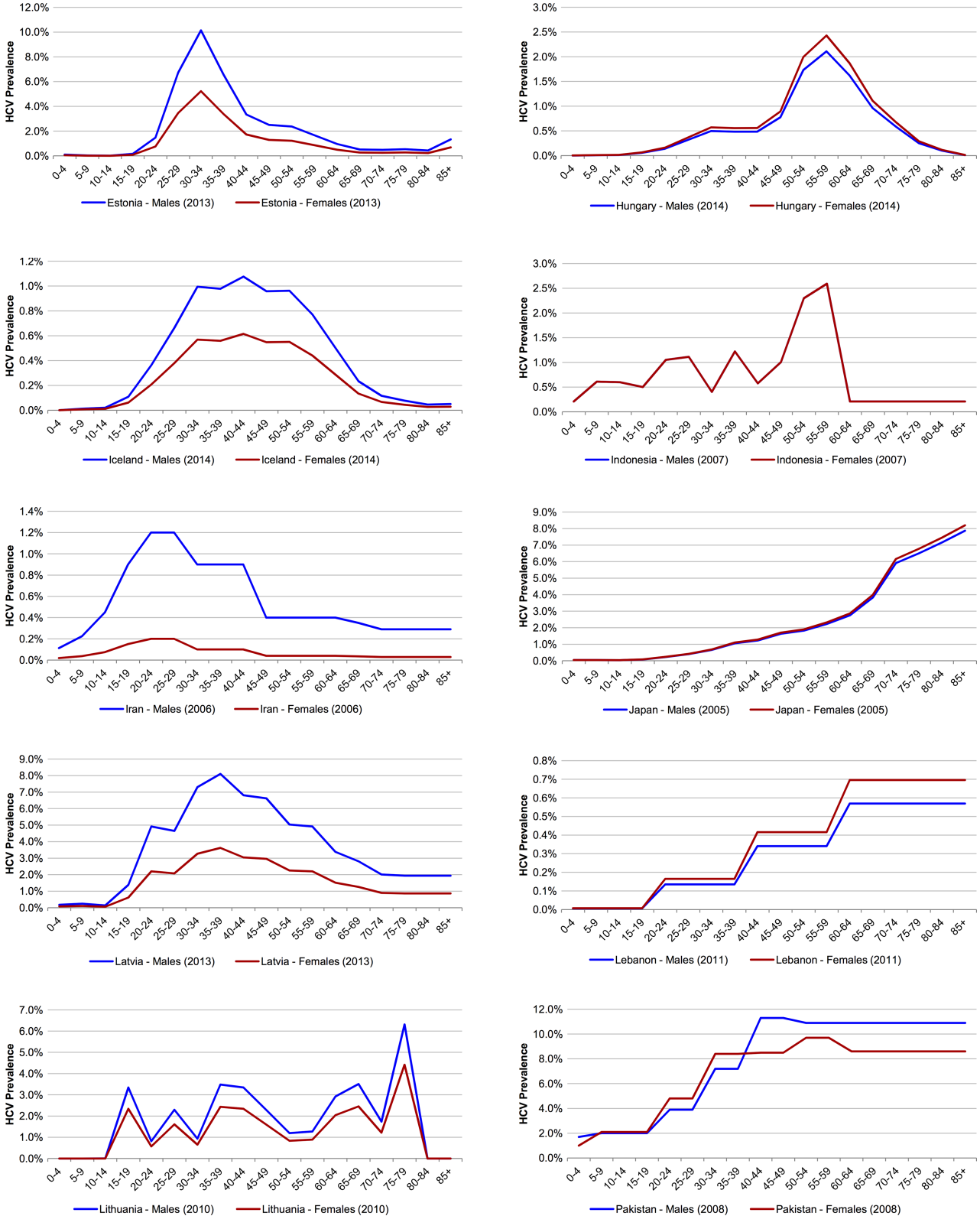

Fig. 1 Viraemic hepatitis C virus (HCV) prevalence by age and gender.

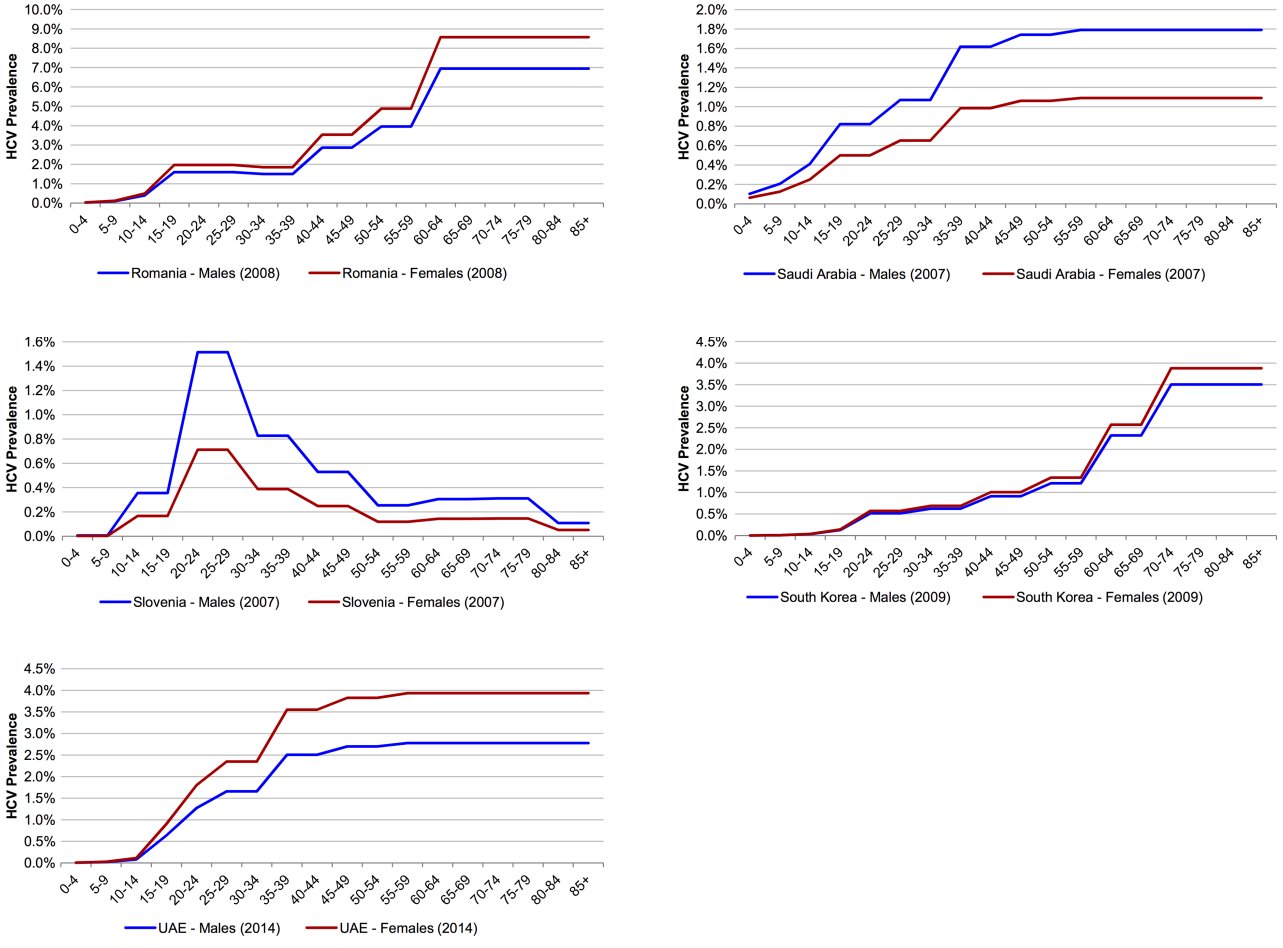

Fig. 1 *(continued)*

distribution of the prevalent population was estimated using unpublished laboratory data from 494 cases in Iceland collected by the Department of Virology at Landspitali University Hospital, while the distribution of G1 subtypes was based on data from the same source during an earlier time period.

Diagnosed

The total number of anti-HCV diagnosed cases is estimated at 1230, with 865 diagnosed after adjustment for mortality, viraemia and treated and cured. The newly diagnosed population in 2013 was estimated at 70, with approximately 60 newly diagnosed after adjustment for viraemia.

Treated

It was estimated that 25–30 patients were treated annually based on overall treatment levels between 2002 and 2012, during which a total of 207 patients received treatment.

Liver transplants

From 1985 to 2013, a total of 45 patients underwent liver transplantation in Iceland. Two transplants during this time period were attributable to HCV (4%).

Indonesia

HCV-infected population

The 2007 anti-HCV prevalence was estimated to be 0.8% (range 0.1% in Sumatra Barat to 1.7% in Nanggroe Aceh Darussalam), using the National Basic Health Research (RISKESDAS) 2007 study [21]. The viraemic rate was estimated to be 66% based on an older study [22]; however, this estimate is in line with more recent unpublished estimates (expert consensus). This corresponds to a viraemic prevalence of 0.5% (0.1–1.1%) in 2007, or 1 214 000 (182 000–2 534 000) infected individuals. The age and gender distribution was estimated using data from RISKESDAS 2007 [21]; however, it is important to note that the data are from the West and middle of Indonesia and are not necessarily representative of the entire country. Genotype 1 predominates in Indonesia, followed by G3. The genotype distribution (G1: 68%, G2: 9%, G3: 9%, G4: 4%, G other: 10%) was determined by averaging genotypes from three unpublished data sources, including a study in HIV-coinfected patients to account for under-represented populations (Lesmana, Muljono and Yunihastuti 2015 personal communications).

Diagnosed

Based on Indonesian Red Cross data and expert consensus, there were estimated to be 121 000 viraemic individuals (approximately 10% of the viraemic-prevalent population) with a known diagnosis of chronic HCV in 2013. Between 2007 and 2009, the Ministry of Health reported approximately 18 000 individuals diagnosed with HCV. Applying this annual number of diagnosed cases to the years 1992–2007 would suggest that by 2009 a total of 90 000 anti-HCV or 59 100 viraemic individuals had been diagnosed. Additionally, from 2010 until 2014, The Indonesian Red Cross notified between 8400 and 12 100 individuals of an HCV diagnosis annually through blood donation, or approximately 35 500 viraemic-diagnosed individuals and notified over five years (Syafitri 2015 personal communication). Overall, this suggests a total of 94 600 diagnosed and reported viraemic cases. Considering that some diagnosed cases would not be reported to the Ministry of Health or via blood donation, an overall diagnosis rate of 10% was estimated at approximately three times the number of known diagnosed cases. Approximately 12 100 viraemic cases were newly diagnosed annually, based on an estimate of 11 000 known cases and assuming a small number of unreported cases.

Treated

It was estimated that 230 patients were treated annually based on IMS data for standard units of Peg-IFN sold after adjustment to account for under-reporting and increased treatment of genotype 2 patients.

Liver transplants

Liver transplants are uncommon in Indonesia, as many patients travel abroad for a transplant. In one large hospital in Jakarta, there have been a total of 13 liver transplants performed (Gani 2015 personal communication). None of the patients treated were infected with HCV (Gani 2015 personal communication).

Iran

HCV-infected population

In 2006, a population-based study across three provinces estimated the antibody prevalence of HCV in adults aged 18–65 to be 0.5% [23]. When adjusted to include all ages, the anti-HCV prevalence in Iran is estimated to be 0.4% (0.3–0.5%), representing 275 000 (189 000–360 000) individuals in 2006. Utilizing a widely published viraemic rate of 62%, there is a viraemic prevalence of 0.2% (0.2–0.3%) representing approximately 170 000 (117 000–223 000) viraemic persons in 2006 [24]. The population-based study provided a reliable age and gender distribution [23]. Where data were lacking for the age and gender distribution, expert consensus was utilized. In Iran, the dominant genotype is 1, followed by genotype 3 [25].

Diagnosed

Based on expert opinion, it was estimated that there are 60 000 individuals diagnosed with HCV in Iran in 2013. It is estimated that there are 6000 individuals newly diagnosed annually.

Treated

Through expert consensus, it was estimated that there were 4500 individuals treated for HCV in 2011.

Liver transplants

Actual liver transplant data were available through IRODaT, with 590 liver transplants occurring in 2013. In Iran, 16% of all liver transplants are due to HCV, corresponding to 94 HCV-related liver transplants in 2013 [26].

Japan

HCV-infected population

The viraemic-prevalent population in 2011 was estimated to range from 1 010 000 to 1 510 000 individuals (equivalent to a viraemic prevalence of 0.8–1.2%). Based on ratios between base, high and low viraemic prevalence reported for 2005 [27], the base viraemic prevalence in 2011 was estimated at 1.0% (1 252 000 cases). With a viraemic rate of 70% [28], anti-HCV prevalence in 2011 was estimated at 1.4% (1 789 000 cases). The age and gender distribution of the infected population in 2005 was based on reported prevalence rates among individuals aged 5–74 years [27]. It was assumed that prevalence in the 0–4 year age group was equal to that of 5- to 9-year-olds. Prevalence among individuals aged 75+ years was assumed to increase as compared to younger individuals based on a trend of increasing prevalence with age. A male/female ratio of 0.96 was applied based on reported prevalence rates by gender [28]. The genotype distribution of the prevalent population was estimated using laboratory data from 494 cases in Japan, while the distribution of G1 subtypes was based on data from the same source during an earlier time period.

Diagnosed

The total number of viraemic undiagnosed cases was estimated at 296 000 cases in 2011 [27]. With 1 252 000 viraemic cases in 2011, the previously diagnosed viraemic population was estimated at 956 000. Based on expert consensus, the newly diagnosed viraemic population in 2014 is estimated at 8000.

Treated

Based on IMS unit for Peg-IFN sold in 2012, it was estimated that 26 900 patients were treated annually.

Liver transplants

Total annual liver transplants from 1989 to 2011 were reported by the Japanese Liver Transplantation Society

[29]. The proportion attributable to HCV varied by year and ranged from 0% to 54%. In 2011, there were an estimated 219 liver transplants attributable to HCV.

Latvia

HCV-infected population

A 2008 population-based study in Latvia identified an anti-HCV prevalence of 2.4% (95% CI 1.7–3.3%) in the general population [30]. These data also suggest a viraemic rate of 71%, corresponding to a 1.8% (1.2–2.4%) viraemic prevalence in the total population (39 000 in 2008) [30]. The age and gender distribution was estimated using annual notification data from 2010 to 2014 (partial year 2014) [31]. The notified populations was aged to the year 2013, accounting for mortality and cured patients.

Diagnosed

As of 2008, approximately 17 000 of the 39 000 viraemic cases were diagnosed (42.5%) [32]. From 2010 to 2014, an average of 1300 chronic HCV cases were newly diagnosed [33].

Treated

In 2014, approximately 840 patients were treated for HCV with Peg-IFN and RBV. The number of patients treated annually between 2011 and 2014 was available from the National Health Service [34]. Additionally, the number of patients treated annually at the Infectology Center of Latvia was available for 2005–2014 (Tolmane 2015 personal communication).

Liver transplants

Liver transplants are not reimbursed by the government, and there has only been one liver transplant ever conducted in Latvia [20,32]. A long waiting list exists for transplants, and some patients (including children) have chosen to travel abroad for the procedure (expert consensus).

Lebanon

HCV-infected population

The most up-to-date data from 2010 to 2011 report an anti-HCV prevalence of 0.2% among all ages in the general population in Lebanon [35]. Low (0.1%) and high (0.7%) prevalence estimates were chosen from the literature [36,37]. A viraemic prevalence of 0.2% (0.1–0.6%) was calculated using the viraemic rate of 85% from the same study [35], corresponding with 7900 (2800–28 000) viraemic cases in 2011. The general population study was used to apply an age distribution and male-to-female ratio [35]. Unpublished data on 1030 HCV-infected patients from 2012 to 2013 determined the genotype distribution between genotypes 1 and 4, but the G1 subtype distribution came from a 2007 study [38].

Diagnosed

Data on number of HCV cases diagnosed in Lebanon are sparse. The Ministry of Health reports incomplete data, and there is no published literature on the annual number of diagnosed cases. Experts estimated that approximately 20% of all viraemic cases have been diagnosed, with 2% of viraemic cases diagnosed each year. This corresponds to approximately 1600 previously diagnosed cases and 160 newly diagnosed cases annually in 2014.

Treated

Data were obtained from the Ministry of Public Health on number of patients treated in 2013–2014, and expert input estimated this accounted for approximately 45% of all treated cases. Pharmaceutical audit data were used to estimate number treated from 2007 to 2012. It was estimated that 280 patients were treated in 2013 and 170 in 2014.

Liver transplants

Liver transplants are very rare in Lebanon. Data from the one hospital that performs transplants reported 15 transplants between 1999 and 2008, with only one due to HCV (6.7%) [39,40]. Experts estimate an additional 6–8 transplants were performed on Lebanese patients each year in foreign countries. Four transplants were performed and reported in Lebanon in 2013 [20].

Lithuania

HCV-infected population

A national seroprevalence survey was underway in Lithuania in 2010–2013. Although initial results from 2010 (anti-HCV prevalence of 2.85% among adults) have been published [41], there has been concern that the individuals seeking free testing in this first year were more likely to be at high risk of infection (Liakina 2015 personal communication). Preliminary results including 2010 and going through 2013 are currently unpublished but suggest an anti-HCV prevalence of 1.96% (1.21–2.71%) in adults 18–81 years of age (Liakina 2015 personal communication). When extrapolated to the entire population (all ages), an overall estimated anti-HCV prevalence of 1.7% (1.0–2.3%) was considered for 2013. These data also suggest a viraemic rate of 66%, corresponding to a 1.29% viraemic prevalence among adults 18–79 years, or 1.1% (0.7–1.5%) in the total population (33 000 in 2013) (Liakina 2015 personal communication). The age distribution was informed by initial 2010 results (5-year age-cohort) [41] and unpublished 2010–2013 results (average age of 47 ± 16 years) (Liakina 2015 personal communication). Approximately 54% of anti-HCV-positive individuals are male [41]. Of note, unpublished results suggest asymptomatic HCV-RNA carriers were younger (38.3 ± 15.5 years) and more evenly distributed by gender (52.6% males), as compared with the anti-HCV-positive population.

The 2003–2009 genotype distribution was estimated using data from 125 treatment naïve patients enrolled in the chronic hepatitis C cohort [42]. Additionally, the genotype 1a/1b split was available from 2000 patients admitted for antiviral treatment to the Center of Hepatology, Gastroenterology and Dietetics at Vilnius University Hospital Santariškių Klinikos between 1996 and 2006 [43].

Diagnosed
Estimates of the diagnosed and newly diagnosed populations were unavailable, so the percentage of diagnosed cases in Poland (15%) in 2010 was chosen as an analogue, with 10% newly diagnosed annually (expert consensus). This corresponds to approximately 5000 total diagnosed and 500 annual newly diagnosed cases in 2010.

Treated
Accurate estimates of treated patients were not available; however, expert opinion suggested that between 300 and 600 patients have been treated annually since 2004 (Valantinas 2015 personal communication). The mid-point of 450 patients was chosen for the model.

Liver transplants
The annual number of liver transplants was available from IRODaT from 2002 to 2014 [20,44]. Of the 101 total liver transplants performed in Lithuania, 40 (40%) were attributable to HCV (Valantinas 2015 personal communication).

Pakistan

HCV-infected population
Pakistan has previously been identified as one of the three countries with the highest number of viraemic HCV infections in the world [45]. In 2008, there was a nationwide estimate on antibody prevalence of HCV infection corresponding to 4.8% [46]. A range of 3.5–5.9% was chosen by expert opinion. This rate corresponds to 8 010 000 (5 792 000–9 920 000) individuals infected with HCV in 2008. Utilizing a widely published viraemic rate of 87.4%, there is a viraemic prevalence of 4.2% (3.0–5.2%), representing approximately 7 001 000 (5 062 000–8 670 000) viraemic persons in 2008 [47]. The data from the aforementioned national study also provided a reliable age and gender distribution for the infected population. Data from a systematic review of 34 papers published between 1996 and 2011 were used to establish the genotype distribution [48].

Diagnosed
Based on expert opinion, it was estimated that 15% of the viraemic HCV-infected population had been diagnosed in 2010, corresponding to approximately 1 050 000 viraemic-diagnosed individuals. It is estimated that there are 100 000 individuals newly diagnosed annually.

Treated
It was estimated that there were 85 000 individuals treated in 2011. This was based on an analysis of standard and Peg-IFN units sold in Pakistan.

Liver transplants
Based on expert opinion, it is estimated that an annual 300 Pakistanis receive liver transplantation both domestically and abroad, with 75% of these transplants attributed to HCV [49,50].

Romania

HCV-infected population
The most recent HCV prevalence estimate in Romania was 3.23%, or 529 100 anti-HCV cases, among adults aged 18–69 in 2008 [51]. This estimate, applied to the entire population, increases to an anti-HCV prevalence of approximately 3.3%, or 719 000 cases. An anti-HCV prevalence range of 2.9–3.6% was chosen by expert input. A viraemic rate of 85% was determined by expert consensus, corresponding to a viraemic prevalence of 2.8% (2.5–3.1%) and 611 000 (541 000–680 000) viraemic cases in 2008. A nationwide study of the adult population determined the age distribution for 18- to 69-year-olds [51], and experts estimated that the prevalence rate would remain at the rate for 60- to 69-year-olds for adults over the age of 70. Based on expert consensus, the rates for the younger age groups (10–14, 5–9, 0–4) decreased by 25% with each successive age group. A genotype distribution study from 241 viraemic individuals from 2004 to 2008 found that the vast majority of cases were type 1b, followed by type 1a [52]. Only 1.20% of cases were found to be genotype 4, and 0.8% of cases were found to be genotype 3 [52].

Diagnosed
Based on expert consensus, there are an estimated 7500 viraemic cases diagnosed per year in Romania, and there have been an estimated 90 000 previously diagnosed cases.

Treated
In 2014, approximately 4100 new patients were treated in Romania, which is the lowest number of treatment initiations in the country since 2007 (Gheorghe 2015 personal communication). In 2013, for example, 6086 treatments were initiated (Gheorghe 2015 personal communication).

Liver transplants
Liver transplant data for 2000–2013 were available through the International Registry for Organ Donation and Transplantation and the Romania National Transplant Agency [20,44,53]. Expert consensus determined that the

number of liver transplants in 2014 was 124, a slight increase from the reported 122 transplants in 2013. Between 2000 and 2011, 27% of transplants in Romania were attributable to HCV [54].

Saudi Arabia

HCV-infected population

The prevalence rate of anti-HCV in Saudi nationals aged ≥15 years was estimated at 1.08% (0.97–1.19%) based on expert consensus, with a much lower prevalence rate among children (0.19%). Overall, the prevalence in Saudi nationals was estimated to be 0.7% (0.6–0.9%). A viraemic rate of 70% was applied [55], resulting in a viraemic prevalence rate of 0.5% (0.4–1.3%) among all ages and a total viraemic population of approximately 100 000 (81 000–257 000) individuals in 2011. The age distribution was based on data from 28 000+ blood units collected in a donor study conducted in the Jazan region from 2004 to 2009 [56] and then modified via expert input, specifically regarding ages >60 years. A male/female ratio based on a prevalence study of 1482 subjects in the Gizan area screened for HCV [57] was applied. Genotype distribution was applied from a meta-analysis of 18 genotype studies in Saudi Arabia [58] with genotype 1 subtype estimates provided by expert consensus.

Diagnosed

Data on the number of diagnosed HCV cases in Saudi Arabia are limited. The percentage of viraemic cases previously diagnosed was estimated at 20% in 2013 based on expert input. Cases newly diagnosed in 2013 were estimated to account for 10% of those previously diagnosed cases, or 3% of all viraemic cases. Thus, the total number diagnosed in 2013 was estimated to be 20 100 cases, with 2010 of those newly diagnosed that year.

Treated

It was estimated that 1900 Saudi nationals were treated annually in 2009 based on expert input and adjusting for immigrant patients. IMS data for standard units of Peg-IFN sold were used to estimate number treated from 2006 to 2009. The standard treatment in Saudi Arabia as of 2014 was Peg-IFN and ribavirin.

Liver transplants

In 2012, there were 146 liver transplants performed in Saudi Arabia according to data collected at a national organ transplantation centre from 1990 to 2012 [59]. It was estimated that 98% of these transplants were performed on Saudi nationals based on expert input. Nearly half of all liver transplants in Saudi Arabia were attributable to patients with HCV according to expert consensus.

Slovenia

HCV-infected population

The real HCV prevalence remains unknown in Slovenia as no national survey has been performed. HCV prevalence in the total population was estimated at 0.4% (0.3–0.5%) based on expert input. A study of 72% of all patients who were diagnosed with chronic HCV in Slovenia from 1993 to 2007 found a viraemic rate of 78% in 2007 [60], corresponding to a viraemic prevalence of 0.3% (0.2–0.4%), or 6500 (4900–8100) viraemic cases in 2014. The age and gender distribution was developed using data from the 1993–2007 study analysing 1504 serum samples (72.6% of all the patients diagnosed with hepatitis C in that period) that had been collected and processed on the national level at the referential laboratory for viral hepatitis of the Medical Faculty University of Ljubljana [60]. The highest rate of anti-HCV prevalence was found in 21- to 30-year-olds, and there was an overall ratio of 67.3% males to 32.7% females [60]. The genotype distribution of the infected population was also derived from the 1993–2007 study, with the majority of cases testing as genotypes 1 and 3 [60]. Ratios of genotype 1 subtypes 1a to 1b were determined using data from a study on pregnant women in Slovenia in 1993, 2003, 2009 and 2013 and were applied to the 1993–2007 genotype data [60,61].

Diagnosed

Expert consensus during a 2015 National Viral Hepatitis Expert Group panel in Slovenia estimated the number of previously diagnosed viraemic cases to be 3300 (Matičič 2015 personal communication). It is estimated that 5% of total diagnosed cases, or approximately 170 cases, are newly diagnosed each year.

Treated

HCV treatment in Slovenia is performed at five treatment centres in five regions of Slovenia, with the Clinic for Infectious Diseases and Febrile Illnesses at the University Medical Centre Ljubljana representing the referential centre. The National Viral Hepatitis Expert Group set up consensus guidelines for HCV treatment in 1997 and has been updating them regarding the Standard of Care [62]. The data on all the treated patients in Slovenia regarding treatment efficacy and safety have been collected and periodically analysed since 1997 [63,64]. The 2015 National Viral Hepatitis Expert Group panel came to the consensus that 1700 patients had already been treated as of March 2015 (Matičič 2015 personal communication). The number of treated patients in 2014 was estimated to be 150, based on expert input.

Liver transplants

Unpublished national liver transplant data between 1998 and 2014 from the National Viral Hepatitis Expert Group

indicate that approximately 7% of liver transplants during this period were attributable to HCV (Matičič 2015 personal communication). In 2014, there were 31 liver transplants performed, an increase of 35% from the highest number of transplants performed in recent years (Matičič 2015 personal communication).

South Korea

HCV-infected population

The most recent estimate of anti-HCV prevalence among adults was 1.2% in 2013, a slight reduction from 1.29% in 2009 [65]. This corresponds to 1.0% prevalence in the general population. Low (0.8%) and high (1.3%) prevalence estimates were chosen from the literature [65,66] The viraemic rate was estimated to be 56%, corresponding to a viraemic prevalence of 0.6% (0.4–0.7%) in 2009 and 268 000 (211 000–349 000) infected individuals [66]. The age and gender distribution was estimated from a nationwide seroepidemiology survey of adults ≥20 years, in which the average age was 54 years [66]. For children and adolescents under 20 years of age, an accelerated reduction in prevalence was assumed. The genotype distribution was established from a study of 930 patients in the HCV cohort [67].

Diagnosed

As of 2012, approximately 93 600 viraemic cases were diagnosed (35%) (expert consensus). Annually, 8000 viraemic cases (3% of the total population) are newly diagnosed (expert consensus).

Treated

It was estimated that 4500 patients annually were treated based on expert consensus and IMS data for standard units of Peg-IFN sold after adjustment to account for under-reporting and increased treatment of genotype 2 patients.

Liver transplants

Liver transplant data for 2000–2011 were available through the Korean Network for Organ Sharing [68]. Prior to 2000, the number of transplants and percentage of transplants attributable to HCV (2.5%) were available through published estimates [69]. Indications for liver transplant were available from 2009 to 2013 through the Korean Network for Organ Sharing, which suggests that approximately 5% of liver transplants were attributable to HCV [68].

UAE

HCV-infected population

HCV epidemiology data are limited in the United Arab Emirates (UAE). Expert consensus estimates the prevalence of anti-HCV to be 1.5% (1.4–1.7%) among all ages of UAE nationals. A viraemic rate of 68% [70] was applied, resulting in a total viraemic population estimate of 11 000 (10 000 – 12 000) and a viraemic prevalence rate of 1.0% (0.9–1.1%) among UAE nationals. In the absence of data on age distribution, analogue data were used from 28 000+ blood units collected in a donor study conducted in Saudi Arabia from 2004 to 2009 to estimate the age distribution [71]. Based on expert input, age distribution was modified to peak around age 45 years and remained at a constant rate from that age forward. A male/female ratio was applied using unpublished data from Mafraq hospital in Abu Dhabi. Genotype distribution (including genotype 1 subtypes) was determined by aggregating data from a study of 124 UAE nationals in Dubai [72] and unpublished data from a hospital in Abu Dhabi and weighted by regional population.

Diagnosed

Expert consensus estimates that one-third of the viraemic population had been diagnosed in 2014. Using analogue data from Egypt, approximately 3% of viraemic cases were newly diagnosed in the same year [7]. It was estimated that a total of 3600 UAE citizens had been diagnosed as of 2014, including 360 newly diagnosed cases that year.

Treated

It was estimated that 140 patients were treated annually from 2011 based on expert consensus.

Liver transplants

Expert consensus approximates that around 30 liver transplants are performed each year with 20 of those performed on nationals. Experts estimate 60% of liver transplants are due to HCV.

DISCUSSION

This analysis was designed to develop consensus estimates for the epidemiology of HCV infection in the countries under study. Published data from each country were identified through an initial literature search. Those results were then discussed and reviewed with an expert advisory panel in each country. Where possible, the members of the advisory panel also provided additional data including hospital and national-level data as well as unpublished study data. This method of developing consensus estimates allowed for a more complete picture of HCV epidemiology to be developed, even in countries where national prevalence studies may not yet have been performed. In-depth review of all data with an advisory panel of experts in the field of HCV within each country also increased the accuracy of each analysis.

Given the substantial global disease burden associated with HCV, it is imperative that reliable epidemiological data are available so that policy makers can make the

most informed decisions possible for their respective countries. As higher efficacy treatments (SVR > 90%) with fewer side effects and shorter treatment durations become available, countries are faced with challenging public health policy questions about changing national treatment paradigms, such as the impact of limiting treatment to patients in certain disease stages. Data from this study can be used by researchers and policy makers to examine how best to combat HCV through further disease burden modelling, analysis of risk factors including the impact of immigration, and the creation of the most appropriate prevention, screening and treatment strategies.

Anti-HCV prevalence estimates in the countries represented in this study range from as low as 0.2% of the population in Lebanon to 4.8% in Pakistan. Figure 1 shows the age and gender distribution of HCV prevalence in each country. Examining the distribution in this manner allows for an analysis of the main risk factors associated with HCV infection. Countries where injection drug use (IDU) is the main source of new HCV infections (e.g. Iceland, Iran and Slovenia) generally display a higher prevalence in men of younger age groups, whereas countries where infection was historically related to an unsafe blood supply or nosocomial transmission (e.g. Japan, Pakistan and South Korea) generally display a higher prevalence in older age groups. Genotype distribution also varied widely between countries. This heterogeneity in genotype distribution is observed even among the countries in one region, which mainly reflects differences in HCV epidemiology, modes of transmission and ethnic variability. For example, Genotype 1 is the most common genotype in Iran, while Genotype 3 is prominent in Pakistan and Genotype 4 is the most common genotype in Saudi Arabia. Overall, Genotype 1 is the most common, accounting for over 80% of cases in some countries. However, it is difficult to make comparisons of genotype, age and gender distributions across countries, as estimates from the literature span a period of over 20 years. Comparison of HCV epidemiology across all countries in 2014 is the subject of another paper in this supplement [13].

Although a prevalence estimate was gathered for every country, the quality of estimates varied. A quantitative scoring system [73] was not used to compare the quality of prevalence figures, but national surveillance and general population studies in Indonesia, Latvia, Lebanon, Lithuania, Pakistan and Romania were more robust than consensus estimates. While the development of consensus estimates provides the best estimates of HCV epidemiology through the combination of all available data and expertise within a specific country, this method also has the potential for some biases. In countries where limited or no data were available, the estimates used in this analysis were based on the consensus of the advisory panel and therefore may not accurately represent the actual HCV epidemic in the country.

Furthermore, data used from registries or specific epidemiological studies may introduce a selection bias to this analysis, as testing and reporting may not be consistent across all subpopulations and would likely not be representative of hard-to-sample populations such as IDU.

It is important to note that the viraemic rate and genotype distributions often came from studies with small sample sizes, and in many countries, the genotype distribution is rapidly changing due to differences in historical risk factors compared to the risk factors currently driving the epidemic.

When data were not available for the number of treated patients within a country, estimates were based on drug sales data. In the absence of better information, the estimated number of treated patients by genotype was determined using the genotype distribution of the infected population. In some cases, these estimates still might be over- or under-estimates of the true treatment numbers genotype as some genotypes may be preferentially treated.

While this analysis is based on the best available data, the limitations inherent in these consensus estimates underscores the need for additional research to be conducted to further estimate the true HCV burden among both the general population and specific subpopulations who might be missed in a national study.

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